Atty. Dkt. No. 029318-0973

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: H. William Bosch et al.

Title: NOVEL NIMESULIDE COMPOSITIONS

Appl. No.: 10/697,703

Filing Date: 10/31/2003

Examiner: Tristan J. MAHYERA

Art Unit: 1615

Confirmation Number: 8369

DECLARATION UNDER 37 CFR 1.131

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, H. William Bosch, hereby declare and state that:

1. I am a citizen of the United States, residing at 237 Rodney Circle, Bryn Mawr, PA 19010.

2. At the time of events detailed in paragraph 4, *infra*, I was an employee of Elan Drug Delivery, Inc., with offices at 3500 Horizon Drive, King of Prussia, PA 19406.

3. I am a co-inventor of the invention disclosed and claimed in the above-referenced application.

4. Prior to June 27, 2003, I instructed my associates, as part of my supervisory role, to prepare nimesulide compositions comprising particles of nimesulide or a salt thereof having an effective average particle size of less than 2000 nm and at least one surface stabilizer adsorbed on the surface of the particles. My work relating to preparing the nimesulide compositions, which occurred prior to June 27, 2003, is documented in the attached exhibits.

5. As shown in Exhibit A (Notebook No. 5822, pages 006-008), the formulation comprising 5% nimesulide and 1% Plasdone® S-630 provides a stable nanoparticulate nimesulide composition.

6. As shown in Exhibit B (Notebook No. 5822, pages 009-011), the formulation comprising 5% nimesulide and 1% Plasdone® S-630 provides a stable nanoparticulate nimesulide composition.

7. As shown in Exhibit C (Notebook No. 5822, pages 012-014), the formulation comprising 5% nimesulide, 1% Plasdone® S-630 and 0.2% DOSS provides a stable nanoparticulate nimesulide composition.

8. As shown in Exhibit D (Notebook No. 5822, pages 015-017), the formulation comprising 5% nimesulide, 1% Plasdone® S-630 and 0.05% sodium lauryl sulfate (SLS) provides a stable nanoparticulate nimesulide composition.

9. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent resulting therefrom.

June 27, 2008
Date

H. William Bosch
H. William Bosch

Title Nimesulide (5% API ; 1% S-630)

(cont. from pg. 005)

Batch Record for Dispersion Technology Milling Procedures

I. General Information

Name	Christian Werty
Date	
Formula	5% - Nimesulide 1% S-630
Continued on Page	007

II. Quantities Dispensed

	Quantity	Type	Source	Lot Number
Media	80.6	Polymill 200	Dow / PMRS	
Drug Substance	4.25	Nimesulide	Sigma	
Stabilizer	0.85	S-630		
Water	79.9	DI		
Other				

III. Process Parameters

Milling Method	Dyno mill (150 cc batch chamber) F915 @ Rm. 205
Mill Speed	4,200 rpm
Temperature	~10°C

IV. Notes

Milling Time:	9:53 – Start milling ; 10:39 – first sample
	10:53 – Second sample ; 11:41 – third sample
	1:10 – Harvest
Quantity retained post-milling:	forgot to filter out media before weighing

* Did not filter out media initially and discarded ~½ suspension. Later filtration left ~20 mL of media free suspension.

(cont. on pg. 007)

Signature Christian Werty Date

Reviewed and understood by Kris Ryde Date

Title Nimesulide (5% API ; 1% S-630)

(cont. from pg. 006)

Batch Record for Dispersion Technology Milling Procedures

Name	Christian Wertz
Date	
Formula	5% Nimesulide 1% S-630
Continued from page	006

IV. Particle Size Data

Particle Size Analyzer Used	HORIBA LA-910 (S# 85148701030)
Standards Measured	Lot # 22579 ; mean = 200 ; Duke Sci ; 200 nm Std

Elapsed Time	Mean, nm	D50, nm	D90, nm	Comments
46	173	156	285	No Sonication
	169	148	280	60 sec. Sonication
60	150	124	256	No Sonication
	144	121	243	60 sec. Sonication
108	3461	140	14961	No Sonication
	131	111	218	60 sec. Sonication
197	10794	318	33156	No Sonication
	140	112	246	60 sec. Sonication
3 day	195	142	339	No Sonication
	143	115	249	60 sec. Sonication

* Particles begin to aggregate ~~after~~ between 60 - 108 minutes
* Caused by reduction in particle size (increase in surface area) which could not be compensated for with 1% S-630
* Can increase S-630 concentration or add additional Stabilizer
* Particle size data in folder #2

(cont. on pg. 008)

Signature Christian F. Wertz Date

Reviewed and understood by Michael Rader Date

Title Nimesulide (5% API, 1% S-630)

(cont. from pg. 007)

Particle Size Stability for Dispersion Technology Formulations

I. General Information

Name	Christian F. Wentz
Date	
Formulation	5% Nimesulide 1% S-630
Notebook reference	
Continued on page	

II. Particle Size Data

Particle Size Analyzer Used	HORIBA LA-910 (S# 851487 0103D)
Standards Measured	Lot # 22569; mean = 200 nm; Duke Sci; 200nm Std.

Elapsed Time	Storage Conditions	Mean, nm	D50, nm	D90, nm	Comments
3 days	5°C	195	142	339	No Sonication
	5°C	143	115	249	60 sec. Sonication
5 days	5°C	176	119	322	no Sonication
	5°C	138	113	235	60 s Sonication
7 days	5°C	194	116	342	no Sonication
	5°C	139	110	248	60 s Sonication
14 days	5°C				
	5°C				

• Data in ~~folder #2~~ Supplementary folder OFN-5822A

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(cont. on pg._____)

Signature Ch. F. Wentz Date

Reviewed and understood by W. William Bosch Date

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LABORATORY NOTEBOOK NO. 5822 Page 009 of 200

Title Nimesulide (5 % API, 2 % S-630)

(cont. from pg. _____)

- mix S-630 slowly into DI H2O w/ mild stirring until dissolved
- add polymill 200 w/ gentle manual stirring
- add API w/ gentle stirring until thoroughly mixed

Batch Record for Dispersion Technology Milling Procedures

I. General Information

Name	Christian Wertz
Date	
Formula	5 % Nimesulide, 2 % S-630
Continued on Page	010

II. Quantities Dispensed

	Quantity	Type	Source	Lot Number
Media	80.6	Polymill 200	DOW	MM00/012
Drug Substance	4.25	Nimesulide	Sigma	117H1019
Stabilizer	1.70	S-630	ISP Tech.	ML900012974
Water	79.05	DI		
Other				

III. Process Parameters

Milling Method	Dyno mill (150 cc batch chamber) F915 @ Rm 205
Mill Speed	4200 rpm
Temperature	~10 °C

IV. Notes

Milling Time: 8:15 Start batch; 9:15 1st sample.
10:15 2nd Sample; 11:15 Harvest
Quantity retained post-milling: 49.6 g (58 %)

(cont. on pg. 010)

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Signature Christian Wertz Date

Reviewed and understood by R. William Bosch Date

Title Nimesulide (5% API, 2% S-630)

(cont. from pg. 009)

Batch Record for Dispersion Technology Milling Procedures

Name	Christian Wertz
Date	
Formula	5% API, 2% S-630
Continued from page	009

IV. Particle Size Data

Particle Size Analyzer Used	HORIBA LA-910 (S# 85148701030)
Standards Measured	Lot # 22529; mean=200 nm; Duke Sci. 200 nm Std.

Elapsed Time	Mean, nm	D50, nm	D90, nm	Comments
60	156	136	255	ND Sonication
	156	134	258	60 S sonication
120	125	109	201	no sonication
	122	107	193	60 S Sonication
180	144	111	260	no Sonication
	132	111	221	60 S Sonication

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· Data in ~~folder #2~~ Supplementary folder OFW-5822 A

(cont. on pg. 011)

Signature Christian F. Wertz Date

Reviewed and understood by D. William Bosch Date

Title Nimesulide (5% API, 2% S-630)

(cont. from pg. 010)

Particle Size Stability for Dispersion Technology Formulations

I. General Information

Name	Christian NPNTS
Date	
Formulation	5% API, 2% S-630
Notebook reference	
Continued on page	

II. Particle Size Data

Particle Size Analyzer Used	HORIBA LA-910 (S# 85148701030)
Standards Measured	Lot # 22589; mean = 200 nm; Duke Sci.; 200 nm Std.

Elapsed Time	Storage Conditions	Mean, nm	D50, nm	D90, nm	Comments
1 day	5°C	141	111	253	no sonication
	5°C	130	110	215	60 S sonication
3 day	5°C	138	111	242	no sonication
	5°C	129	110	215	60 S sonication
7 day	5°C	145	113	258	no sonication
	5°C	134	112	226	60 S sonication
21 day	5°C	154	123	272	no sonication
	5°C	141	116	241	60 S sonication
35 day	5°C	153	125	266	no sonication
	5°C	145	121	246	60 S sonication

· Data in folder ~~#2~~ cfw supplementary folder CFW-5822 A

(cont. on pg.)

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Signature Christian F. Wirth Date

Reviewed and understood by W. William Bosch Date

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LABORATORY NOTEBOOK NO. 5822 Page 012 of 200

Title Nimesulide 5% API, 1% S-630, 0.2% DOSS

(cont. from pg. _____)

Batch Record for Dispersion Technology Milling Procedures

I. General Information

Name	Christian F. Wertz
Date	
Formula	5% API, 1% S-630, 0.2% DOSS
Continued on Page	013

II. Quantities Dispensed

	Quantity	Type	Source	Lot Number
Media	80.6	polymill 200	DOW	MM001012
Drug Substance	4.75	Nimesulide	Sigma	117H1019
Stabilizer	0.85	S-630	ISP Tech.	ML900012974
Water	79.73	PI		
Other	0.17	DOSS	Cytec	SD0041815

III. Process Parameters

Milling Method	Dynomill (150 cc batch chamber) F915 @ room 205
Mill Speed	4200 rpm
Temperature	10 C

IV. Notes

Milling Time: 8:20 Start batch ; 9:20 1st Sample
11:20 Harvest
Quantity retained post-milling: 26.12g (30.7 %)

- Solution was significantly less viscous w/ DOSS than previous runs
- Dissolved S-630, then dissolved DOSS w/ gentle stirring (~ 15 min)
- Slight leak when mill was started - some solution lost

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(cont. on pg. 013)

Signature Christian F. Wertz Date

Reviewed and understood by William Bosch Date

Title Nimesulide 5% API, 1% S-630, 0.2% DOSS

(cont. from pg. 012)

Batch Record for Dispersion Technology Milling Procedures

Name	Christian F. Wertz
Date	
Formula	5% API, 1% S-630, 0.2% DOSS
Continued from page	012

IV. Particle Size Data

Particle Size Analyzer Used	HORIBA LA-910 (s#: 8514870103D)
Standards Measured	Lot #: 22569; mean = 205 ; Duke Sci.; 200 nm standard

Elapsed Time	Mean, nm	D50, nm	D90, nm	Comments
60	172	154	278	no sonication
	172	156	280	60 s sonication
120	131	111	216	no sonication
	130	110	217	60 s sonication

• Data in ~~folder #1~~ qfw Supplementary folder CFW-5822 A

(cont. on pg. 014)

Signature Christian F. Wertz Date

Reviewed and understood by William Bosch Date

Title Nimesulide 5% API, 1% S-630, 0.2% DOSS

(cont. from pg. 013)

Particle Size Stability for Dispersion Technology Formulations

I. General Information

Name	Christian F. Wertz
Date	
Formulation	5% API, 1% S-630, 0.2% DOSS
Notebook reference	
Continued on page	

II. Particle Size Data

Particle Size Analyzer Used	HORIBA LA-910 (s#: 8514870103D)
Standards Measured	Lot #: 22569; mean = 203 ; Duke Sci.; 200 nm standard

Elapsed Time	Storage Conditions	Mean, nm	D50, nm	D90, nm	Comments
1 day	5°C	136	116	223	no Sonication
	5°C	137	116	224	60 s Sonication
2 day	5°C	143	121	238	no sonication
	5°C	144	122	241	60 s Sonication
5 day	5°C	149	133	239	no Sonication
	5°C	151	135	242	60 s Sonication
7 day	5°C	160	143	259	no Sonication
	5°C	163	146	261	60 s Sonication
21 day	5°C	162	150	252	no Sonication
	5°C	166	155	255	60 s Sonication
35 day	5°C	180	172	276	no sonication
	5°C	187	180	280	60 s sonication

Data in ~~folder #C~~ cfw Supplementary folder CFW-5822 A

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(cont. on pg.)

Signature Christian F. Wertz Date

Reviewed and understood by R. William Bosch Date

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LABORATORY NOTEBOOK NO. 5822 Page 015 of 200

Title Nimesulide 5% API, 1% S-630, 0.05% SLS

(cont. from pg. _____)

- Dissolved S-630 in H_2O followed by SLS under gentle mixing
- SLS dissolved very rapidly w/ very little foam

Batch Record for Dispersion Technology Milling Procedures

I. General Information

Name	Christian F. Wertz
Date	
Formula	5% API, 1% S-630, 0.05% SLS
Continued on Page	

4. Quantities Dispensed

	Quantity	Type	Source	Lot Number
Media	80.6	Polymill 200	DOW	MM001012
Drug Substance	4.25	Nimesulide	Sigma	117H1019
Stabilizer	0.85	S-630	ISP Technology	ML900012974
Water	79.86	H2O	DI	
Other	0.04	SLS		

III. Process Parameters

Milling Method	Dynomill (150 cc batch chamber) F915 @ room 205
Mill Speed	4200 rpm
Temperature	10 C

IV. Notes

Milling Time: 8:22 Start batch; 9:22 1st Sample
10:22 Harvest
Quantity retained post-milling: 69.4 g (80.7 wt %)

- Mill began leaking after first sample was taken from mill

(cont. on pg. 016)

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Signature Christian F. Wertz Date _____

Reviewed and understood by W. William Bosch Date

Title Nimesulide 5% API, 1% S-630, 0.05% SLS

(cont. from pg. 015)

Batch Record for Dispersion Technology Milling Procedures

Name	Christian F. Wertz
Date	
Formula	5% API, 1% S-630, 0.05% SLS
Continued from page	

IV. Particle Size Data

Particle Size Analyzer Used	HORIBA LA-910 (s#: 8514870103D)
Standards Measured	Lot #: 22569; mean = 200 ; Duke Sci.; 200 nm standard

Elapsed Time	Mean, nm	D50, nm	D90, nm	Comments
60	174	154	288	no Sonication
	176	157	291	60 S Sonication
120	116	104	175	no Sonication
	117	105	178	60 S Sonication

Data in ~~folder #2~~ Supplementary folder OFN-5822 A

(cont. on pg. 017)

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Signature Christian F. Wertz Date

Reviewed and understood by W. William Bosch Date

Title Nimesulide 5% API, 1% S-630, 0.05% SLS

(cont. from pg. 016)

Particle Size Stability for Dispersion Technology Formulations

I. General Information

Name	Christian F. Wertz
Date	
Formulation	5% API, 1% S-630, 0.05% SLS
Notebook reference	
Continued on page	

II. Particle Size Data

Particle Size Analyzer Used	HORIBA LA-910 (s#: 8514870103D)
Standards Measured	Lot #: 22569; mean = ; Duke Sci.; 200 nm standard

Elapsed Time	Storage Conditions	Mean, nm	D50, nm	D90, nm	Comments
3 day	5°C	123	108	192	no Sonication
	5°C	123	108	193	60 s Sonication
5 day	5°C	127	110	203	no Sonication
	5°C	127	110	205	60 s Sonication
7 day	5°C	133	113	217	no Sonication
	5°C	134	113	219	60 s Sonication
21 day	5°C	126	110	199	no Sonication
	5°C	127	109	205	60 s Sonication
35 day	5°C	141	120	234	no Sonication
	5°C	142	119	237	60 s Sonication

Data in ~~folder #1~~ supplementary folder CFW-5822 A

(cont. on pg.)

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Signature Christian F. Wertz Date

Reviewed and understood by W. William Bosch Date